REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. Claim 1 has been amended. The specification has been amended to correct obvious typographical errors and to incorporate material by reference. New claims 9-12 have been added. No new matter has been added through the amendments. Claims 1-12 are currently pending. Applicants respectfully request reconsideration and withdrawal of the pending rejections under 35 U.S.C. §112, first paragraph, and 35 U.S.C. §103.

Claims

Claim 1 has been amended. Support for the amendment is found throughout the specification, including paragraphs 10 and 78. New claims 9-12 have been added. Support for the amendments are found throughout the specification, including paragraphs 93 (claim 9), 95 (claim 10), 96 (claim 11), and 97 (claim 12). No new matter has been added through the amendments or the new claims.

Specification

The Examiner objects to the incorporation of material in the specification by reference to a foreign application or patent or publication. The specification has been amended in order to include the material incorporated by reference. Applicants enclose an Affidavit, executed by the applicant's Canadian patent agent, stating that the amendatory material consists of the same material incorporated by reference in the disclosure.

The specification has been reviewed and amended to correct typographical errors.

In view of the amendments, Applicants request reconsideration and withdrawal of the objections to the specification.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejects claims 1-8 under 35 U.S.C. §112, first paragraph, for an alleged lack of enablement. The Examiner contends that the scope of the claims is not commensurate

with the scope of enablement in the specification. Specifically, the Examiner asserts that pyridoxal-5'-phosphate for the treatment of ischemia does not reasonably provide enablement for other types of 3-acylated analogues of pyridoxal. Applicants respectfully traverse.

The instant application teaches and claims the use of pyridoxal-5'-phosphate (P5P), pyridoxal, pyridoxamine, or 3-acylated pyridoxal analogue together with a therapeutic cardiovascular compound in the treatment of hypertrophy in a mammal. Pyridoxal, pyridoxamine, or the 3-acylated pyridoxal analogue *in vivo* metabolization to pyridoxal-5'-phosphate was well known at the time of filing.

Applicants have sufficiently enabled the genus of 3-acylated pyridoxal analogues. A specification is not required to disclose every example or species covered by a claim, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976). In the instant specification, Applicants have disclosed the genus of 3-acylated pyridoxal analogues and have exemplified several species, including ones of formula I and formula II at pages 8-10 of the specification. To require Applicants to disclose every species would be unduly burdensome and is not required under existing case law. Accordingly, the specification provides an enabling disclosure to make and use the genus of 3-acylated pyridoxal analogues.

Applicants respectfully disagree with the Examiner's position that undue "painstaking experimentation study" is necessary to determine all of the analogues or derivatives of pyridoxal-containing compositions enabled in this specification. Such a determination is not necessary. The analogues will metabolize to pyridoxal-5'-phosphate. Thus a selection of an analogue is not a burden and does not involve any undue experimentation.

In addition, the Examiner's attention is directed to the fact that the priority application, now US 6,677,356, issued with claims of scope similar to the ones rejected by the Examiner in this application.

Accordingly, Applicants respectfully request reconsideration and removal of the rejection under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §103

A. Haque

The Examiner has cited US 6,339,085 of Haque, who is also a named inventor in this application, and has stated that claims 1-8 are obvious in view of this patent. The Examiner has indicated that the rejection under 35 USC 103(a) may be overcome by a showing under 37 CFR §1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and thus is not inventive "by another". In response, we enclose an Affidavit under 37 CFR §1.132 by the present inventor, demonstrating that any invention disclosed but not claimed in U.S. Patent No. 6,339,085 was derived from the inventor of this application and thus is not an invention "by another".

B. Smith in view of DiPiro

The Examiner has cited WO 98/19690 of Smith et al. and a chapter in the book Pharmacotherapy, Pathophysiologic Approach of Editor DiPiro, and has stated that the claims are obvious over Smith in view of DiPiro. The Examiner has taken the position that it would have been obvious to a person skilled in the art to employ compositions containing vitamin B_6 and its related analogues such as pyridoxamine and pyridoxal-5'-phosphate or other structurally related compounds of pyridoxine, as well as ACE inhibitors and angiotensin II antagonists known to treat microvascular events that lead to hypertrophy. Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, three criteria must be met--a suggestion or motivation to combine references, a reasonable expectation of success, and the prior art reference teaches or suggests all the claim limitations. MPEP §2143; *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). There is no motivation to combine Smith *et al.* with DiPiro and no suggestion of all the claim limitations in the cited references. The Applicants respectfully assert that the Examiner has not met the criteria for establishing obviousness under 35 U.S.C. §103(a).

Smith *et al.* teach that one of the causes of the microvascular events leading to ischemia in the medial temporal lobe is a moderate deficiency in vitamin B_{12} and folate. The deficiency in vitamin B_{12} and folate leads to elevated homocysteine levels in the plasma because vitamin B_{12}

and folate are required cofactors in the conversion of homocysteine to methionine. Homocysteine can have a toxic effect on the blood vessels that initiate the pathological cascade process leading to changes in the microvasculature. Smith *et al.* teach the administration of angiotensin-converting enzyme (ACE) inhibitors, such as enalapril, to treat high blood pressure. Smith *et al.* also teach that the administration of ACE-inhibitors and angiotensin II antagonists are known to reduce the damage to the endothelium and to the elastic laminae in arterioles caused by homocysteine. In addition, Smith *et al.* disclose that ACE-inhibitors are known to potentiate the response of the endothelium to agonists that increase the release of endothelium-derived relaxing factors, such as nitric oxide. Smith *et al.* specifically teach the concurrent administration of vitamin B_6 or B_{12} in combination with an ACE inhibitor or an angiotensin II antagonist in order to modify the deleterious effects of ***homocysteine*** on the vasculature.

However, Smith *et al.* do not disclose the use of pyridoxal-5'-phosphate, pyridoxal, pyridoxamine, or any 3-acylated analogue of pyridoxal in the indicated therapy. Only vitamin B_6 and other compounds non-relevant to the present invention are used in Smith *et al.* Although pyridoxal-5'-phosphate, pyridoxal, pyridoxamine and 3-acylated analogues of pyridoxal are derivatives of vitamin B_6 (pyridoxine), they are different compounds, with chemical structures and metabolic properties distinct from vitamin B_6. In addition, there is no suggestion in the disclosure of this reference that vitamin B_6 derivatives were contemplated. Indeed, reference is made to "folic acid or a folate or a derivative thereof or betaine or vitamin B_6 or a combination thereof, above, or optionally with vitamin B_{12},...". *See* page 5, lines 9-12. In the case of folic acid or a folate where derivatives thereof are contemplated, a list of such derivatives is specifically disclosed. *See* page 7, lines 1 through 9. This list does not disclose any compounds of the instant application.

Further, vitamin B_6 (pyridoxine) is not pharmaceutically equivalent to the active metabolites. Although there are metabolic pathways from all of the vitamin B_6 precursors to pyridoxal-5'-phosphate, the metabolically active form of the vitamin is not equivalent. For example, the administration of pyridoxine results in high plasma levels of pyridoxine, which can lead to toxic effects such as peripheral neuropathy (Schaumburg *et al.*, *New England J Med* 1983, 309, 445-448). Pyridoxal phosphate itself is less effective than pyridoxal in reducing

ischemia induced neuronal damage (Yamashima *et al.*, *Nutr. Neurosci.* 2001, 4(5), 389-397). Pyridoxamine specifically inhibits the formation of advanced end glycation products, which contribute to the chemical modification of proteins during aging and diabetes (Onorato *et al.*, *J. Biol. Chem*, 2000, 275(28), 21177-21784). Pyridoxal-5'-phosphate has been found to alleviate epileptic seizures which do not respond to treatment with pyridoxine (Kuo and Wang, *Pediatr. Neurol.*, 2002, 26(2), 146-7). Since Vitamin B_6 is not pharmaceutically equivalent to the active metabolites in the instant application, the cited references have not suggested all of the claim limitations.

Additionally, there is no motivation to combine the DiPiro reference with Smith *et al.* The DiPiro reference provides an overview of congestive heart failure and teaches that congestive heart failure can be the result of many causes including hypertension and vasoconstriction. "Hypertrophy of the ventricle ***may*** produce dramatic changes in compliance, even though each individual muscle unit may have relatively normal passive length-tension relations." DiPiro does not disclose the use of pyridoxal-5'-phosphate, pyridoxal, pyridoxamine, or any 3-acylated analogue of pyridoxal in the treatment of congestive heart failure or hypertrophy. In fact, the DiPiro reference teaches away from the instant application. Table 11.3 lists "drugs that may exacerbate or precipitate congestive heart failure." Included in this list are β-blockers (propranolol and others) and calcium channel blockers (verapamil and others). Applicants respectfully assert that the combination of Smith *et al.* and DiPiro would only result from hindsight reconstruction. *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992). There is no motivation to combine Smith *et al.* with DiPiro.

C. Smith in view of Lobel

The Examiner rejects claims 1-8 as being unpatentable over Smith *et al.* in view of US 3,282,778 of Lobel. The Examiner has not, however, indicated how the Lobel patent is applied against the claims of this application.

The teachings of Lobel relate to medical preparations for the administration of medicines via oral and parenteral routes, which comprise among other substances, a non-toxic pyridoxine compound. Lobel only presents evidence relating to combining aspirin with a pyridoxine

compound for the treatment of colds and combining fluoride with a pyridoxine compound for the treatment of dental carries. Lobel, at best, only provides speculation on the therapeutic advantage of combining a cardiovascular drug with a pyridoxine compound. Lobel does not attribute any medicinal value to pyridoxine derivatives; they simply act as a vehicle to increase the rate of absorption of actual drug. Applicants are the first to show medicinal value from treatment with pyridoxal-5'-phosphate. Therefore, Applicants demonstrate unexpected results over the teaching of Lobel. Further, the combination of pyridoxal-5'-phosphate in combination with other hypertensive agents is a novel treatment method. Applicants respectfully submit that the teachings of this patent are not relevant to the patentability of the claims of the instant application.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

Obviousness-Type Double Patenting Objection

The Examiner has raised an obviousness-type double patenting objection in relation to claims 1 and 3-8 in view of US 6,339,085 of Haque. Additionally, the Examiner has required Applicants to show that the conflicting inventions were commonly owned at the time of invention. In response, Applicants enclose a copy of assignment agreements for the cited reference and the present application, which show that the invention was owned by the same entity at the relevant time. The Examiner has also raised a provisional obviousness-type double patenting objection in relation to claims 1-2 and 4-8 in view of co-pending applicant's Application Serial No. 09/863,093. Applicants acknowledge the Examiner's rejections for obviousness-type double patenting. Upon indication of allowance, Applicants will file a terminal disclaimer if appropriate.

In view of the above amendments and remarks, Applicants respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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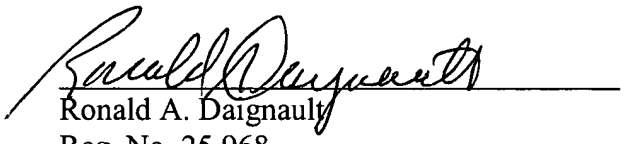

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